ABSTRACT

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Biochemical Sciences

Candidate: Jana Holubová
Supervisor: prof. RNDr. Lenka Skálová, Ph.D.
Title of diploma thesis: Metabolism of flubendazole in human liver subcellular fractions

Flubendazole (FLU), a benzimidazole anthelmintic drug with a broad spectrum of activity and low toxicity has been used in veterinary as well as human medicine for a long time. Owing its mechanism of action, based on the specific binding to tubulin, FLU is now considered a promising anti-cancer agent. However, we do not have enough information about its biotransformation in human.

In our project, subcellular fractions from the liver of 12 human patients (6 males and 6 females) were used to study the stereospecificity, cellular localization, coenzyme preference and possible inter-individual or sex differences in FLU reduction. In addition, the risk of FLU interaction with other drugs was evaluated. Results showed that FLU is predominantly reduced in cytosol and the NADPH coenzyme is preferred. The strict stereospecificity of FLU carbonyl reduction was proven and carbonyl reductase 1 was identified as the main enzyme of FLU reduction in the human liver. A higher reduction of FLU and a higher level of carbonyl reductase 1 protein was found in males than in females, but overall inter-individual variability was relatively low. Hepatic intrinsic clearance of FLU is very low, and FLU had no effect on doxorubicin carbonyl reduction in the liver and in cancer cells. For these reasons, interactions of FLU with other carbonyl bearing drugs are not expected. The obtained results demonstrate the safety of FLU use in human and support FLU repurposing for cancer treatment.